WS17.5 Evaluation of antibiofilm activity of new homoserine lactones (HSL) analogs of *Pseudomonas aeruginosa*

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Objectives: *Pseudomonas aeruginosa* can cause severe lung infections in patients with cystic fibrosis, particularly in establishing a resistant structured form called biofilm. Biofilm formation is mainly regulated by the communication system of the Quorum Sensing (QS), controlled by the natural *N*-acyl homoserine lactones (HSL) molecules. Thus, the aim of our study is to design potent HSL analogs to inhibit this biofilm development.

Methods: Various analogs, based on the structure of C4-HSL, were synthesized and screened for their ability to impair biofilm formation in an innovative model developed in the laboratory. Among them, compound C11 (N-pymimidyl butanamide) showed a significant inhibition of biofilm formation in a dose-dependent manner, coupled with an absence of cytotoxicity on lung cells. Moreover, its inhibitory activity was preserved on a biofilm developed under anaerobic conditions, set up to approximate the *in vivo* colonization conditions by the bacterium. Then, C11 was tested in association with antibiotics and a significant synergistic effect was obtained with ciprofloxacin, tobramycin and colistin. After a structure-activity study performed on C11, new analogs were synthesized and two showed an interesting antibiofilm activity.

Conclusion: To improve these results, we propose to synthesize and to screen new analogs, based on the structure of C4-HSL, and then of 3-oxo-C12-HSL, in order to affect all QS mechanisms. Thus, this study should allow to determine the best combination of effective molecules against the *P. aeruginosa* biofilm and to define optimal conditions for further *in vivo* investigations.

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WS17.6 Phase 3 trial of inhaled levofloxacin (Aeroquin™, MP-376, APT-1026) vs. tobramycin inhalation solution (TIS) in intensively treated CF patients over 6 months

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Introduction: The development of new effective inhaled antibiotics is an important therapeutic need. Aeroquin (AQ) is a novel levofloxacin formulation for inhalation by a customized nebulizer using eFlow technology. This Phase 3 study assessed the efficacy and safety of AQ compared to TIS in CF patients with chronic *P. aeruginosa* (PA).

Methods: Randomized, open-label trial of three cycles (28-days on/28-days off) of 240 mg BID AQ vs. TIS 300 mg BID. Patients were ±12 yrs, chronic PA lung infection, FEV_1 from 25–85% pred, and ⩾3 TIS courses in the previous year. The 1° endpoint was a non-inferiority (NI) margin of 4% in relative change in FEV_1 % pred at Day 28. 2° endpoints included changes in absolute FEV_1, CFQ-R resp. domain, sputum PA density, and time to exacerbation, anti-PA antibiotics and hospitalization.

Results: Of 282 patients enrolled, 272 were dosed, 33 (11.7%) discontinued. Mean patient baseline age was 28.5 yr; FEV1 was 54.5% predicted. Patients averaged 5.9 inhaled antibiotic courses in the previous year. The 1° endpoint of NI was met; the LS mean difference in relative change in FEV_1% pred between groups at Day 28 was 1.86% in favor of AQ (95% CI –0.66, 4.39). Similar results were observed at the end of treatment at Days 84 and 140. AQ resulted in longer time to need for anti-PA antibiotics and greater CFQ-R respiratory domain scores. No statistical significance between groups was observed for time to exacerbation (Fuchs) or hospitalization. Group AE and SAE incidence was similar.

Conclusion: The primary endpoint of NI comparing AQ to TIS was met. These data suggest AQ has a similar therapeutic effect to TIS which is sustained over 3 treatment cycles.